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ORIGINAL PAPER

Peripheral biomarkers to predict the diagnosis of bipolar disorder from major depressive disorder in adolescents

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Abstract

The onset of bipolar disorder (BD) occurs in childhood or adolescence in half of the patients. Early stages of BD usually present depressive episodes, which makes it difficult to be distinguished from major depressive disorder (MDD). Objective biomarkers for discriminating BD from MDD in adolescent patients are limited. We collected basic demographic data and the information of the first blood examination performed after the admission to psychiatry unit of BD and MDD inpatients during 2009–2018. We recruited 261 adolescents (aged from 10 to 18), including 160 MDD and 101 BD. Forward-Stepwise Selection of binary logistic regression was used to construct predictive models for the total sample and subgroups by gender. Independent external validation was made by 255 matched patients from another hospital in China. Regression models of total adolescents, male and female subgroups showed accuracy of 73.3%, 70.6% and 75.2%, with area under curves (AUC) as 0.785, 0.816 and 0.793, respectively. Age, direct bilirubin (DBIL), lactic dehydrogenase (LDH), free triiodothyronine (FT3) and C-reactive protein (CRP) were final factors included into the models. The discrimination was well at external validation (AUC = 0.714). This study offers the evidence that accessible information of common clinical laboratory examination might be valuable in distinguishing BD form MDD in adolescents. With good diagnostic accuracies and external validation, the total regression equation might potentially be applied to individualized clinical inferences on adolescent BD patients.

Keywords Bipolar disorder · Major depressive disorder · Adolescent · Diagnosis · Biomarker

Introduction

Bipolar disorder (BD) is a severe chronic mental disorder characterized by recurrent swings of mood states and energy. According to the survey of global burden of disease, there were about 45.5 million BD patients worldwide in 2017, which take up 4.7% of all the mental disorders. Years lived with disability (YLDs) of BD were 9.29 million, around 7.6% of total YLDS of mental disorders [1]. At onset, most BD patients present with depressive episodes. A large proportion of adult BD patients have experienced onset depression episodes at youth. A quantity of 50% – 70% BD patients started to manifest mood symptoms before the age of 21 [2]. Only 20% patients onset with bipolar depressive episodes are correctly diagnosed [3]; for the others, it could be delayed for 8–10 years [4]. Primary symptoms of juvenile bipolar disorder vary a lot from clinical expression of typical adulthood BD. Euphoric mood is rare in adolescent patients, while irritability mood, mixed manic state and chronic course of symptoms are much more frequent, which

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makes it even more difficult to identify BD among young individuals [5].

The most common misdiagnosis is depression. In clinical practice, the diagnostic criteria for a major depressive episode are the same in depression episode of BD and MDD, while there might be some specific symptoms that show a tendency of being associated with each diagnosis: 1) BD exhibits an early onset age (< 25 years), while MDD shows a late onset of first depression (> 25 years). (2) Multiple prior episodes (≥ 5) are frequent in BD, and MDD tends to have long duration of current episode (> 6 months). (3) Patients with BD are more likely to have increases in daytime napping and weight, while for MDD patients, initial insomnia and weight loss are common symptoms. (4) Psychomotor retardation, substance abuse and mood irritability are more frequent in BD, and MDD patients have more somatic complaints as well as the tendency to blame others[6–8]. However, symptom-oriented diagnosis strategy solely is not enough to help recognize BD patients who onset with depression episodes. Therefore, objective diagnostic biomarkers are needed.

Many studies have tried to explore objective diagnostic criteria for adolescent patients with BD. Ideal biological biomarkers are supposed to be objective and applicable tools for early differentiation of BD. In the fields of mental disorders, biomarkers mainly consist of neuroimaging, central and peripheral parameters. Neuroimaging techniques have been applied to explore the abnormalities of white matter connectivity, gray matter, cognitive and emotional neural circuitry that might present in adolescent patients with BD or MDD [9]. As a signal of central nervous system, cerebrospinal fluid (CSF) is helpful for studying the diagnosis and pathogenesis of mental disorders. Numerous studies have devoted to identifying peripheral markers for patients with mental disorder, which mainly include saliva and blood [2]. Peripheral blood is where scientists' interests are mostly focused on. In comparison with blood, CSF seems to be a better source of biomarkers in mental disorders. However, peripheral blood has its own advantages; for instance, it is accessible, quantizable and economic.

Previous studies have revealed that BD and MDD patients present different inflammatory features, as well as metabolic biomarkers in peripheral blood, and oxidative stress markers [10–13]. Brunoni et al. reported that tumor necrosis factor (TNF)-α, soluble TNF receptor (sTNFR)1, Interleukin (IL)-1β, IL-12, and IL-10 were significantly higher in MDD than in BD, whereas IL-6, sTNFR2, IL-18, and IL-33 were significantly higher in BD [14]. The median C-reactive protein (CRP) level was reported to be higher in individuals with bipolar disorder than depression (median 3.5 vs. 2.8 mg/L, $p = 0.01$) [15]. A prior study found higher triglycerides levels in BD patients compared to those with MDD [16]. It has been reported that BD patients showed significantly higher plasma UA levels compared to MDD (337.31 ± 83.56 vs. 220.50 ± 58.36 μmol/L, $p < 0.001$) [17]. Except for above factors, increased serum lactate level of BD and decreased bilirubin level of MDD were also clues for diagnosis of mood disorders [18, 19]. Over the decades, studies have been trying to use serum biomarkers to construct models for aiding clinical practice in the diagnosis of patients with mood disorders [20]. Chang et al. reported that a baseline CRP level of 621.6 ng/mL could help differentiate MDD and BD, with an area under the curve of 0.816, a sensitivity of 0.699 and a specificity of 0.882[21]. Frye et al. reported that transthyretin (TTR, also named prealbumin) was good predictor for BD (ROC-AUC > 0.8) [22]. Moreover, brain-derived neurotrophic factor (BDNF), mature BDNF (mBDNF) and precursor BDNF (preBDNF) in plasma have been reported to be potential differential diagnostic biomarkers for BD and MDD [23].

For now, though numerous markers have been revealed to show differences between BD and MDD, most studies seemed to focus more on adult patients. Evidences of objective markers for adolescents or children are poor, though correct diagnosis is of vital importance. Besides, the application of clinical use is also an important consideration when trying to work out tools for disease diagnosis. This study would like to utilize biochemicals from routine hematological examination of adolescent BD and MDD inpatients as our major parameters to help differentiate the two disorders.

Method

We conducted the cross-sectional, retrospective real-world study in China (Shanghai). The study was approved by Shanghai Mental Health Center (SMHC). The data gathered for this study were from Information Department of SMHC and Hangzhou Seventh People's Hospital. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. Ethical approval of this retrospective research has been obtained from SMHC Institution review board office (2019-15R) and permission to take informed consent is formally waived by approving committee. Patient's personally identifiable information has been cleaned to protect privacy. The clinical trial register number is No. NCT03949218. All methods were carried out in accordance with relevant guidelines and regulations.

Sample

We collected inpatient records of BD or MDD patients who were first-time admitted to SHMC between 2009 and 2018. Discharge diagnosis of all patients met the criteria of

International Classification of Diseases 10 (ICD-10), F31 for bipolar disorder and F32 for major depressive disorder. Demographic data included gender and age. Clinical information primarily focused on the first blood examination after the admission to inpatient unit, which was performed within 15 days after admission. The fasting venous blood was collected between 7:00 a.m. and 8:00 a.m. by a set of standard operating procedures. The inpatients had neither tobacco use nor alcohol consumption at least 18 h before the blood specimen collection. After the blood test, clinical medication and dosing adjustments would be arranged by a doctor-in-charge starting at 8 a.m. every morning. The exclusion criteria include: (1) Patients with abnormal liver function caused by drugs such as valerate and agomelatine. (2) Patients with significant hypothyroidism caused by lithium carbonate. (3) Patients with abnormally increased blood lipids and blood glucose caused by the history of olanzapine. (4) Patients with diabetes and coronary heart. (5) Those had a history of taking blood lipid-lowering drugs. The same criteria were applied to the Hangzhou Seventh People's Hospital for enrollment.

Biochemical indexes mainly consisted of five parts: (i) hematopoietic system, (ii) immune-inflammatory, (iii) liver function, (iv) metabolism, and (v) thyroid and gonadal hormones. All the peripheral bio-parameters were as listed: white blood cell (WBC), neutrophil% (NEUT%), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), hemoglobin (Hb), red blood cell (RBC), platelets (PLT), uric acid (UA), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactic dehydrogenase (LDH), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), globulin (GLO), albumin/globulin (A/G), prealbumin (PA), blood glucose (GLU), total cholesterol (TCHO), high-density lipoprotein (HDL), low-density lipoprotein (LDL), testosterone (Tseto), estradiol (E2), luteinizing hormone (LH), follicle-stimulating hormone (FSH), progesterone (Prog), prolactin (PRL), free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), total thyroxine (TT4), total triiodothyronine (TT3).

Statistical analysis

All data-related procedures were performed in statistical software SPSS 25 version, R (version 3.6.1). Missing data of our selected predictors were under 30%. All the missing values were replaced by mean of nearby points, and span number of nearby points was set as 2. Data analysis included descriptive and inferential statistics approaches. Shapiro–Wilk normality test for parameters was made first. Not all demographic data as well as biochemical indexes were in the Gauss Distribution, and thus, comparisons between BD and MDD were performed via nonparametric test, two independent samples Mann–Whitney U test (skewed distribution data), and Student's t test (normal distribution data). Statistical significance was defined as p value < 0.05 (two-tailed). Box–Tidwell Method was made to test linear relationship between independent and dependent variables. We also checked for multicollinearity among predictors. We used Forward-Stepwise Selection of binary logistic regression models to differentiate BD form MDD with selected biochemical indexes, with criterion of p value 0.05 for entry and 0.10 for removal of variables. And MDD was set as the reference group in the model. Besides, all the patients were grouped by gender, and the same predictors were used to run regression models, respectively. Effect sizes were reported by odds ratios (ORs) with 95% confidence intervals. The Hosmer–Lemershow test was used to assess the calibration of the models. Finally, receiver-operating characteristic (ROC) curves were plotted via probability of each subject and area under curves (AUC) were calculated to estimate the performance of each regression model (0.5 = no discrimination, 0.51–0.69 = poor, 0.7–0.79: acceptable, 0.8–0.89: excellent, ≥ 0.9 = outstanding).

Selection of predictors

The variables in the logistic regression analysis would take those showed significant difference between BD and MDD into account. In addition, as mentioned above, biochemical parameters that are contributed to mood disorders would also be taken into consideration. Of course, as an important factor for both BD and MDD, age would be added in our model.

Results

Comparation of BD and MDD

A total of 261 adolescents (aged from 10 to 18), with 160 MDD (68.9% female, $n = 107$) and 101 BD (50.5% female, $n = 53$) were enrolled in this study. Table 1 summarizes demographic and clinical characteristics of all the participants. BD and MDD patients showed significant gender ($p = 0.04$) and age ($p < 0.01$) difference. In MDD, proportion of female patients is higher than male. Age of first inpatient MDD patients in SMHC during 2009–2018 were younger than that of BD. There were also differences of Hb, UA, ALT, AST, LDH, ALP, GLU, and Testo between groups (p's < 0.05). Hb, UA, ALT, AST, LDH, GLU, and Testo levels of BD were higher than MDD patients. While ALP level of BD is lower. In male subgroup, age, NEUT%, AST, and LDH displayed differences between BD and MDD (p's < 0.05), and BD patients seemed to present higher levels of these indexes (Table S1). For subgroup of female,

Table 1 Demographic and peripheral bio-parameters of participants with BD or MDD

Variable	MDD Mean (SD)	BD Mean (SD)	$\chi 2/Z/t$	p
Age	15.74 (1.62)	16.83 (1.34)	−5.768	< 0.001
WBC (10^9/L)	6.76 (1.83)	7.49 (2.92)	−1.607	0.108
*NEUT%	54.01 (11.86)	56.27 (11.03)	−1.541	0.447
ESR (mm/h)	7.39 (5.80)	6.85 (5.94)	−0.652	0.514
CRP (mg/L)	1.86 (3.72)	2.24 (3.62)	−0.860	0.390
Hb (g/L)	136.04 (15.78)	140.68 (14.90)	−2.612	0.009
RBC (10^{12}/L)	4.67 (0.49)	4.76 (0.47)	−1.727	0.084
PLT (10^9/L)	247.74 (67.18)	243.25 (57.85)	−0.324	0.746
UA (μmol/L)	326.26 (98.39)	360.19 (114.29)	−2.265	0.024
*ALB (g/L)	44.00 (3.40)	43.83 (3.68)	0.382	0.597
TBIL (μmol/L)	14.90 (7.330	16.08 (9.25)	−0.862	0.389
DBIL (μmol/L)	2.65 (1.83)	2.18 (1.35)	−1.681	0.093
ALT (U/L)	18.70 (16.92)	24.52 (20.61)	−3.052	0.002
AST (U/L)	19.28 (7.78)	25.18 (16.39)	−3.850	< 0.001
LDH (U/L)	129.05 (24.87)	154.83 (63.59)	−4.125	< 0.001
GGT (U/L)	14.09 (8.80)	15.16 (8.31)	−1.745	0.081
ALP (U/L)	96.45 (54.55)	80.33 (30.04)	−2.277	0.023
*GLO (g/L)	27.20 (3.43)	27.22 (3.60)	−0.034	0.798
A/G	1.64 (0.23)	1.64 (0.27)	−0.133	0.894
*PA (mg/L)	256.25 (64.09)	255.56 (68.58)	0.079	0.843
GLU (mmol/L)	4.97 (0.86)	5.28 (0.97)	−2.386	0.017
TCHO (mmol/L)	4.29 (0.83)	4.21 (0.83)	−0.900	0.368
TG (mmol/L)	1.06 (0.66)	1.03 (0.88)	−1.460	0.144
*HDL (mmol/L)	1.38 (0.31)	1.36 (0.32)	0.439	0.682
LDL (mmol/L)	2.33 (0.72)	2.28 (0.75)	−0.753	0.451
Testo (nmol/L)	5.85 (8.16)	9.24 (9.98)	−3.310	0.001
E2 (pmol/L)	226.93 (319.20)	188.26 (174.86)	−0.435	0.664
LH (IU/L)	7.28 (6.45)	7.67 (5.57)	−0.679	0.497
FSH (U/L)	4.40 (2.34)	4.63 (2.28)	−0.712	0.476
Prog (nmol/L)	5.64 (11.67)	4.76 (7.12)	−0.742	0.458
PRL (mIU/L)	686.00 (568.40)	761.72 (701.81)	−0.714	0.475
FT3 (pmol/L)	4.66 (1.04)	4.84 (1.13)	−0.802	0.423
FT4 (pmol/L)	15.79 (3.98)	17.15 (4.23)	−1.538	0.124
TSH (mIU/L)	2.55 (2.04)	2.87 (2.16)	−1.189	0.235
TT4 (nmol/l)	89.21 (21.89)	94.55 (24.28)	−0.582	0.561
*TT3 (nmol)	1.64 (0.37)	1.67 (0.41)	−0.486	0.687

*Normal distribution data

differentiators are age, ALB, AST, LDH, ALP, and GLU (p's < 0.05). ALB, AST, LDH, and GLU in female BD subjects showed higher levels than that of MDD (Table S2). However, ALP concentration of female BD patients was lower in comparation with MDD individuals. The levels of rest biochemical indexes in total, male and female patients had no significant differences between the two diseases. Normal range of mentioned biochemical parameters is provided in Table S3.

Regression analysis to identify BD from MDD in adolescents

Finally, we included age, CRP, UA, DBIL, LDH, PA, Testo, and FT3 as our predictors, and Fig. 1 shows the comparation of these selected parameter between BD and MDD (overall sample, male and female subgroups were compared respectively).In total adolescents, BD was best predicted by CRP, UA, DBIL, LDH, PA, Testo, and FT3, as well as age. All these parameters had a linear relationship with dependent variable in logit transformation (Table S4). There was no multicollinearity among independent variables, in that tolerance of these factors were above 0.1 and variance inflation factor (VIF) of them were far below 10 (Table S5). This binary regression model included 261 cases (160 MDD vs. 101 BD), and it showed an AUC of 0.785, and 73.3% accuracy, with a sensitivity of 58% and a specificity of 82.9%. Calibration was obtained by the Hosmer–Lemershow test ($p = 0.671$). Age, DBIL, LDH and FT3 were finally entered into this regression model. The regression equation showed that Age, LDH, and FT3 were negatively correlated with BD diagnosis, while DBIL was positively related (Table S6). The final regression equation for the probability of BD is listed below (P1). Figure 2 displays the ROC curve of this regression model.

$$P1 = 1-1/(1+e(-(-15.378 + 0.620 \times Age - 0.234 \times DBIL + 0.025 \times LDH + 0.409 \times FT3)))$$

Regression analysis to differentiate BD from MDD in gender subgroups

We applied the same parameters to gender subgroups. In male subgroups, the regression equation was finally constructed by Age, DBIL and LDH, in which Age and LDH had negative correlation with BD, while DBIL was positively correlated (Table S7). AUC of this model was 0.816, with accuracy of 70.6%, sensitivity of 72.5% and specificity 68.6%. For female subgroups, the forward stepwise selection logistic regression model enrolled Age, CRP, DBIL, LDH and FT3 as final predictors. Among these indexes, Age, LDH and FT3 were in negative relationship with BD, whereas CRP and DBIL were on the contrary (Table S8). The AUC of regression model for female was 0.793 and 75.2% accuracy, 44.7% sensitivity, with a specificity of 88.7%. The final regression equations for the probability of BD are displayed below (P2 for male, P3 for female). ROC curves of two subgroups are showed in Fig. 2. The Hosmer–Lemershow test showed well calibration of the two models (male $p = 0.937$, female $p = 0.642$).

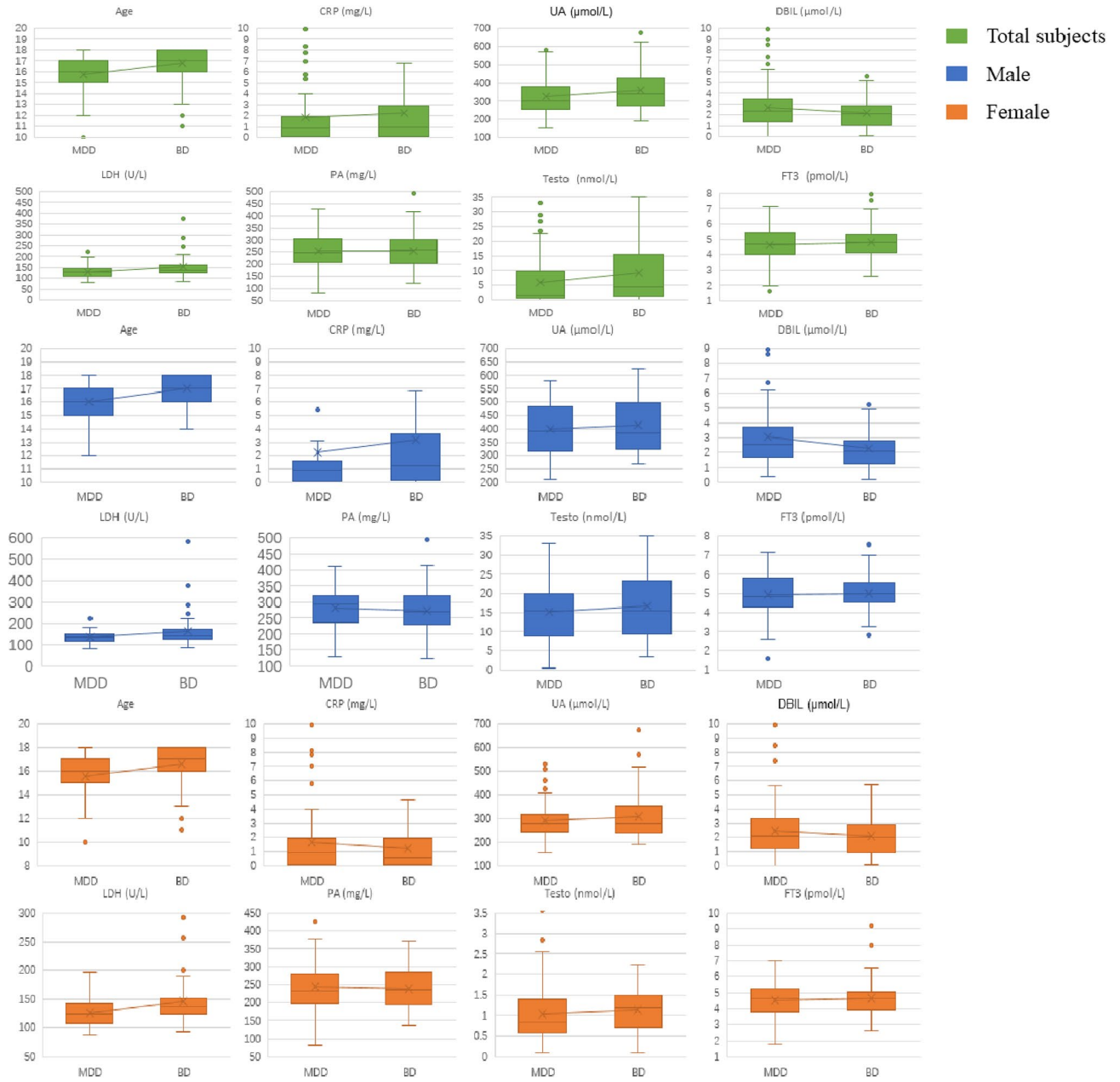

Fig. 1 Comparison of selected parameters between BD and MDD

P2 = 1–1/(1+e(–(–15.809 + 0.797 × Age – 0.368 × DBIL + 0.025 × LDH)))

P3 = 1–1/(1+e(–(–14.378 + 0.492 × Age – 0.293 × CRP – 0.312 × DBIL + 0.036 × LDH + 0.417 × FT3)))

Independent external validation

We obtained information of 802 adolescent patients at Hangzhou Seventh People's Hospital. To validate the model, BD patient at depressive or mixed episodes were selected, while those at mania or hypomanic episodes were excluded. A total of 255 patients, aged from 12 to 18, were finally enrolled (MDD = 172, BD = 83), including 87 male and 168 female patients. The logistic regression equations were applied to all these 255 patients. The percentages of accuracy in classification of total, male and female patients were 73.7%, 60.9% and 78.5%, respectively. The AUCs of the three groups were 0.714 ($p < 0.001$), 0.592 ($p = 0.146$), 0.683 ($p < 0.001$), respectively (Fig. 3).

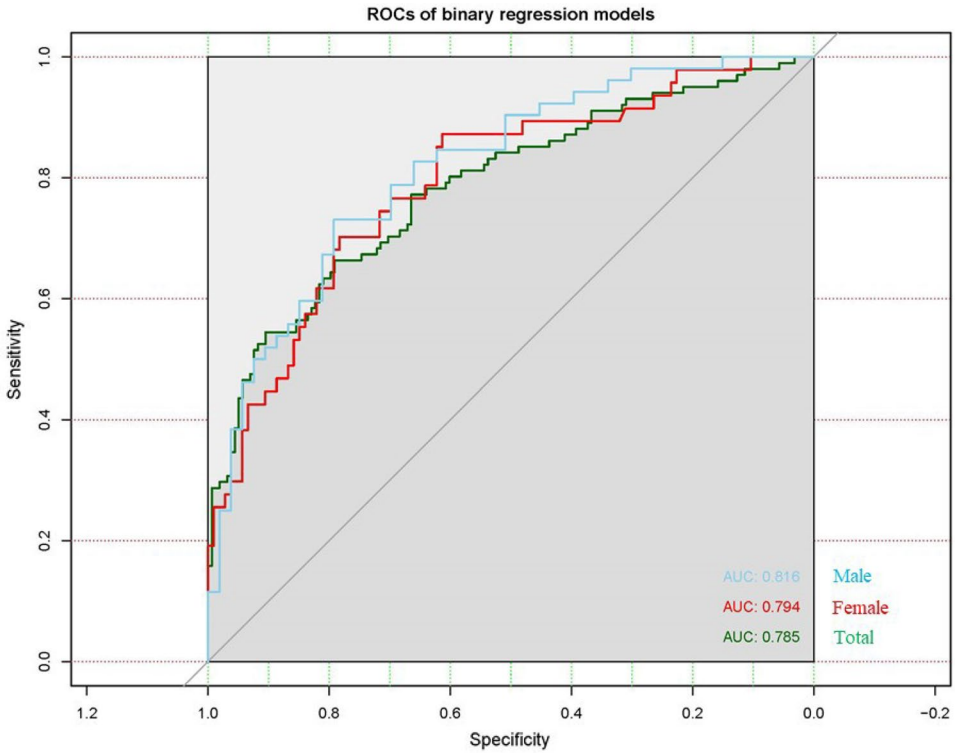

Fig. 2 ROCs of binary regression models of total adolescents, and male and female subgroups

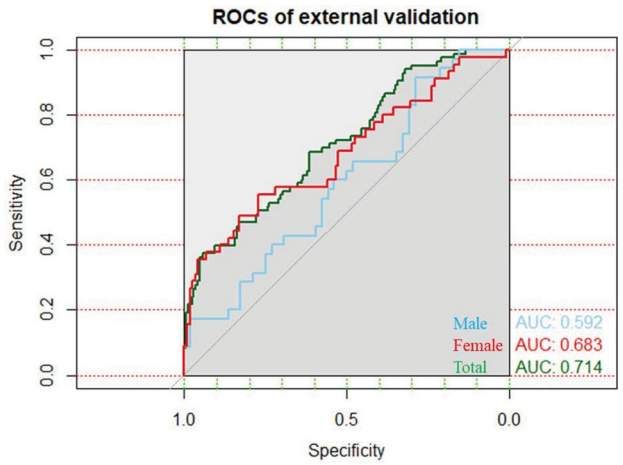

Fig. 3 ROCs of independent external validation of the three models

Discussion

Although abundant previous studies have reported that numerous peripheral parameters were supposed to assist the diagnosis of BD, such as TNF-α and BDNF. However, constructing objective criteria for BD still remains an elusive goal up to now. This study used accessible common clinical information, first-time hematological examination data, of adolescent inpatients in SMHC during 2009–2018 to differentiate BD from MDD. There are gender differences in some of these biochemical indexes, and therefore, analysis of gender subgroups was performed. Binary logistic regression identified that AUC of total adolescent, male and female models were 0.785, 0.816 and 0.793, respectively. Age, DBIL, LDH, FT3 and CRP were contributed to the final regression models, and gender subgroups showed slight difference of enrolled parameters. The total regression equation showed well external validation (AUC = 0.714).

In adolescent, gender distribution of the two diseases showed significant difference. Ratio of female patients was more than that of male in MDD, while for BD, it almost reached the balance. This is what consistent with global prevalence and incidence of MDD [24]. Therefore, gender should be an important factor to take into consideration. However, first hospitalized age of teenage BD patients was slightly older on average than that of MDD, which seemed to be inconsistent with previous evidence of earlier onset of BD [25]. The delayed diagnosis of BD may contribute to it. Besides, inpatient age should not represent onset age.

In hematopoietic system, level of Hb in BD was higher than MDD patients, which is consistent with previous study [26]. Hochman et al. found that BD patients have higher levels of Hb during depressive episode [27]. Interestingly, in subgroups of male and female, no hematopoietic system indexes were found to have difference between BD and MDD. Namely, hematopoietic system itself should not be

effective enough to differentiate BD from MDD. Furthermore, for immune-inflammatory parameters, there was no index founded showing difference between BD and MDD in youth patients and its female subgroup. However, in male subgroup, NEUT% was higher in BD patients. A recent study reported that neutrophil-to-lymphocyte (NLR) was increased in (hypo)mania only among males [28], which suggested that neutrophil might play a role in the pathogenesis of male BD patients. As part of the first innate immune defense line, elevated neutrophils in BD patients suggested that dysregulation of inflammatory might contribute to adolescent BD and MDD patients in different ways. As a matter of fact, the exact mechanism of inflammation's role in the pathogenesis of mood disorders is unclear. Previous evidence proved that MDD can be associated with a sustained low-grade systemic inflammation, especially the somatic or neurovegetative symptoms of depression. While BD is more likely to be associated with a pro-inflammatory state, which is also strongly related to auto-immune diseases [29]. Besides, cytokine levels may vary with mood state changes of BD patients. There is an increase of pro-inflammatory cytokines and a decrease of anti-inflammatory cytokines, while during euthymia, these peripheral changes tend to disappear [30]. Levels of hepatic function indexes ALT, AST and ALP showed significant difference between BD and MDD in adolescents of this study. Among these indexes, ALT and AST were higher in BD, while ALP was higher in MDD. In young male patients, only AST displayed a higher level in BD than MDD. Whereas in young female, levels of ALB and AST were higher in BD patients, and ALP was higher in patients with MDD. However, as is known, indexes of hepatic function are sensitive to antipsychotics and mood stabilizer, such as olanzapine, valproate and lithium. Therefore, in this study, hepatic function-related parameters should not be taken into consideration.

As metabolism parameters, LDH, UA and GLU were found to be statistically different between the two diseases. All of the three indexes were higher in BD. For the subgroup of male, LDH was the only parameter higher in BD. While in teenage female patients, both LDH and GLU were lower in MDD. Strong evidence has supported the role of mitochondrial dysfunction in BD, while lactate is the direct marker for mitochondrial dysfunction [31]. Previous studies have reported that both in brain and cerebrospinal fluid, lactate was significantly elevated in BD compared to healthy controls [32]. And LDH is the primary metabolic enzyme to convert pyruvate into lactate, and vice versa, which is a potential marker for tumor [33]. Thus, accounting for its function in the metabolism of lactate, LDH was involved in the final factors to predict BD. No significant difference of UA concentration was found by gender subgroups in our study, which is inconsistent with previous research [17]. Shenglin et al. have reported that serum UA levels of patients with depression were significantly lower in comparation to patients with schizophrenia, bipolar disorder and healthy controls. This study proved that such a lower level of UA in MDD also exists in adolescent patients. It suggests that teenage patients with depression might present lower antioxidant defense. Adolescents with BD were reported to have high prevalence of metabolic syndrome [34]. While blood glucose is one of the common direct indexes to reflect glycometabolism. Moreira et al. observed higher levels of glucose were in both BD and MDD subjects with current depressive episode compared to healthy individuals [35]. In this study, blood glucose level of BD was even higher than that of MDD. It indicated that the impairment of energy metabolism in BD, as well as dysfunctional mitochondrial oxidative clearance of lactate should be more severe than MDD [36]. Thyroid and gonadal hormones showed no difference in adolescents between the two diseases. However, evidence has suggested that autoimmunity should be an independent risk factor for bipolar BD [37]. And it has been reported that T4 was elevated in both MDD and BD depressed adolescents compared with controls, while T3 was decreased [38]. Such a contradictory result in our study might be due to extremums of the original information. Moreover, promising results have implied that the use of T3 in treatment of bipolar depression could augment and accelerate treatment response of antidepressants and lithium, which might protect against rapid cycling and relapse of BD [39]. On all accounts, hypothalamic–pituitary–thyroid (HPT) axis plays an important role in the pathogenesis and prognosis in mood disorders. Reproductive organs of adolescents are mature gradually, and thus, secretion of sex hormones in them is unstable. It might explain why no gonadal hormones that differs in the two diseases was found in this study. However, in fact, accumulating scientific findings have reported that hypothalamic–pituitary–gonadal (HPG) axis is tending to play a role in the origins of psychiatric symptoms [40]. It has been reported that testosterone can influence neuronal function by binding to intracellular and neurotransmitter receptors, as well as by modulating ligand-gated ion channels. It is also involved in the process of neuronal adaptation to new environmental demands [41]. Furthermore, collected data have showed that estrogen and progesterone closely interact with inflammation pathways and oxidative stress in female patients with BD [42].

Each of the three ROCs showed a good diagnostic accuracy for these models. AUC of total adolescents, teenage male and female were 0.788, 0.796 and 0.811, respectively. However, only the model of total patients showed good external validation, which is expected to be promoted into clinical practice. Regardless of gender difference, the model that counted in all subjects finally enrolled four factors (age, DBIL, LDH, FT3), in which DBIL was a protectively related with BD. While in the model of young male, DBIL was a

positive factor for BD. In female model, both CRP and DBIL were risk factors for BD. Interestingly, no direct evidence has ever demonstrated how DBIL worked in the pathogenesis of BD. As an endogenous antioxidant, bilirubin might also be a clue for the mechanism of BD. Therefore, further pre-clinical and clinical studies are needed. Nevertheless, lower values of TBIL, DBIL and IBIL were observed between patients with MDD and controls [43], which was consistent with this study, so that DBIL could be a negative factor for MDD. What surprised us was that another anti-oxidative marker, UA, was not in the factor list of final models. Further studies of purinergic systemin dysfunction in adolescents with mood disorders are needed. Except for DBIL, in female subgroup, C-reactive protein presented as a risk factor for BD. It is a major acute-phase plasma protein, a member of the pentraxin family, which plays a role in innate immune system of human. A meta-analysis has revealed that CRP concentrations are increased in BD [44]. CRP was only included in the model of female teenage patients, which implied that immune-inflammatory mechanism of mood disorder in young female might be more complicated. It has been reported that reduced secretion of Testo was more common in BD than MDD patients [41]. Interestingly, testosterone was also excluded from the final regression models, which might be due to unmatured development of adolescent. FT3 level was reported to be positively correlated with the score of Hamilton Rating Scale for Depression (HAMD) [41]. In this study, FT3 was found to be positive with the diagnosis of MDD both in total patients and female groups. Further studies are needed to testify how FT3 works in the pathogenesis of mood disorder.

This study enrolled first hospitalized information of adolescents. There are possibilities that their diagnosis for now is wrong, especially for these who are diagnosed as MDD. They might be recognized as BD when growing up. We could not guarantee every patient was medicine-naïve, even though it is their first hospitalization. Medication could have impacts on levels of peripheral biochemical indexes, but the effects of medication were limited with strict enrollment criteria. Besides, hepatotoxicity was proved to be unrelated with adverse hepatic events during maintenance mood stabilizer [45].

In conclusion, accurate diagnosis of bipolar disorder for adolescents is very important. Because delayed proper treatment might result in worse prognosis. In this study, we displayed the biomarkers of first routine hospitalized hematological examination of BD and MDD adolescent patients. These parameters are common biochemical indexed in clinic, which are involved in dimensions of hematopoietic system, immune-inflammatory, hepatic function, metabolism, thyroid, and gonadal hormones. The total predictive model showed good accuracy and external validation for distinguishing BD from MDD. In conclusion, accessible biochemicals from clinical laboratory examination are potential markers to assist early recognize of teenage BD patients, and the total model can be supposed to be further promoted and validated in clinical practice.

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Declarations

Conflict of interest All authors declare no biomedical financial interests or potential conflicts of interest.

Ethical approval Ethical approval of this retrospective research has been obtained from SMHC Institution review board office (2019-15R) and permission to take informed consent is formally waived by approving committee. Patient's personally identifiable information has been cleaned to protect patient privacy. Clinical trial register number was No. NCT03949218.

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